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Review

TRP's: Links to schizophrenia?

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Abstract

Schizophrenia is a chronic psychiatric disorder the cause of which is unknown. It is considered to be a neurodevelopmental disorder that results from an interaction of genetic and environmental factors. Direct evidence for links between schizophrenia and TRP channels is lacking. However, several aspects of the pathophysiology of the disorder point to a possible involvement of TRP channels. In this review evidence for links between TRP channels and schizophrenia with respect to neurodevelopment, dopaminergic and cannabinoid systems, thermoregulation, and sensory processes, is discussed. Investigation of these links holds the prospect of a new understanding of schizophrenia with resultant therapeutic advances.

Keywords: TRP channels; Schizophrenia; Capsaicin; Sensory system; Thermoregulation; Dopamine

1. Schizophrenia

Schizophrenia is a chronic, debilitating psychiatric disorder that afflicts people of all races and carries a life-time risk of the order of 1%. It causes lifelong disability, resulting in major individual and societal cost. Despite extensive investigation, the cause of schizophrenia remains unknown. The complexity of the disorder is reflected in the varying symptomatology. Classically, the positive symptoms, which include delusions, hallucinations and thought disorder, were considered to constitute the major diagnostic criteria of schizophrenia. However, it is now recognized that impaired cognition, particularly in visual memory and working memory, and the negative symptoms of social withdrawal, poverty of speech and anhedonia, are also core symptoms of the disorder [1,2].

Typically the overt signs and symptoms of schizophrenia do not manifest until early adulthood. It is now generally accepted that it is a neurodevelopmental disorder that has its origins in the prenatal or neonatal period, and results from an interaction of both genetic and environmental factors. Recently, the concept has arisen that schizophrenia might result from aberrations in the neuroplasticity phenomena that govern normal brain development and function [3,4]. Several genes have been implicated as susceptibility genes, including neuregulin 1 (NRG1), catechol-*O*-methyltransferase (COMT), dysbindin, disrupted in schizophrenia 1 (DISC1), and regulator of G-protein signaling (RGS) protein-4 (RGS-4), the strongest evidence being for NRG1 [5]. For more detailed information on the neurobiology of schizophrenia and susceptibility genes for the disorder the reader is referred to recent reviews [6–8].

Neuropathological studies on post-mortem human brain have shown that the brains of subjects with schizophrenia are reduced in volume compared with those of healthy individuals [9–11], the frontal lobe being the more severely affected of all four lobes [10]. Furthermore, the brains of subjects with schizophrenia have larger ventricles and thinner cortices, particularly in the prefrontal and temporal regions, than those of normal subjects [12,13]. Selemon et al. [14,15] made the important observation that neuronal density was increased in the prefrontal cortex of subjects with schizophrenia. This finding led to the 'reduced neuropil hypothesis' that the symptoms of schizophrenia result from reduced cortical connectivity rather than a reduction in neuron numbers [16]. Reduced interneuronal space [17], mean cell spacing abnormalities [18], and reduced neuronal size [19] have also been found in the neocortex of subjects with schizophrenia.

The dopamine hypothesis of schizophrenia, which dominated the field for many years, resulted from the observation that stimulants, such as amphetamine that act via release of dopa-

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mine, produced psychosis [2,20], and the discovery of the antipsychotic efficacy of dopamine D_2 receptor antagonists [21]. The roles of the three major dopamine pathways in the central nervous system (CNS), viz. the nigrostriatal pathway projecting from the substantia nigra to the caudate putamen associated primarily with movement control, the mesolimbic and mesocortical pathways projecting from the ventral tegmental area (VTA) to the limbic areas (nucleus accumbens and ventral striatum) and cortex, respectively, associated with schizophrenia and reward, and the tuberoinfundibular pathway important in the inhibition of prolactin secretion, have been extensively investigated over the past three decades [22]. Although the classical dopamine D_2 receptor antagonists were effective in treating the positive symptoms of schizophrenia, they produced serious Parkinsonian-like side effects, presumably due to action on the nigrostriatal pathway as well as on the mesolimbic and mesocortical pathways. Furthermore, they were relatively ineffective in treating the negative symptoms and cognitive impairment of the disorder. The newer atypical antipsychotic drugs have a reduced side effect profile and some efficacy in treating the negative symptoms, but are not effective in treating the cognitive impairment. Thus there is an ongoing search for more appropriate drug targets.

Although the antipsychotic efficacy of D_2 receptor antagonists suggested that the symptoms of schizophrenia resulted from a functional excess of subcortical dopamine, several lines of evidence suggest that there might be a deficit in dopamine in the dorsolateral prefrontal cortex in schizophrenia resulting in impairment of working memory [23]. Since working memory is dependent on D_1 receptor signaling, there has been recent increasing interest in the dopamine system and D_1 receptors in the human cortex [24].

Alterations in markers for several neurotransmitter systems, including the serotonin, gamma-aminobutyric acid (GABA), glutamate and cholinergic systems, have been found in the brains of subjects with schizophrenia. The lack of efficacy of the D_2 receptor antagonists in treating the negative symptoms and cognitive impairment in schizophrenia has led to exploration of the possible roles of these other neurotransmitter systems, albeit with the understanding that any new model will need to provide an explanation for the involvement of dopamine. The hypoglutamatergic hypothesis of schizophrenia has received considerable attention. This hypothesis arose from the observation that administration of *N*-methyl-D-aspartate (NMDA) antagonists, phencyclidine (PCP) and ketamine induced psychotic symptoms and cognitive dysfunction in healthy humans [25–27]. This hypothesis has been supported by the development of a mutant mouse with greatly reduced levels of the NMDA receptor subunit, NR1, which exhibited behaviours considered to be related to schizophrenia, including hyperactivity and impaired social behaviours, that were ameliorated by antipsychotic drugs [28].

2. Overview of TRP channels

The transient receptor potential (TRP) superfamily of ion channels is present throughout the animal kingdom. The members mediate flux of cations across the cell membrane resulting in increased intracellular concentrations of Ca^{2+} and Na^{+}, and depolarization of cells. They are widely expressed in mammalian tissues in both excitable and nonexcitable cells and play an important role in cell signalling. Mammalian TRP channel proteins are characterized by six transmembrane spanning domains with a pore domain between the fifth and sixth domain. The TRP domain is a homologous block of about 25 intracellular amino acid residues adjacent to the C-terminal side of S6 that is loosely conserved in several TRP subfamilies [29,30]. TRP channels are subdivided into six subfamilies on the basis of amino acid sequence homology: TRPA, TRPC, TRPM, TRPML, TRPP and TRPV [31,32]. TRP channels and their structure–function relationships have been reviewed recently [33]. Data from genome sequencing projects suggest that the TRP gene family is now complete [34].

A characteristic of TRP channels is polymodal activation. TRP channels are variously activated by several exogenous natural products such as capsaicin, as well as endogenous chemicals of different structures, including endogenous lipids or lipid metabolites (DAG, phosphoinositides, eicosanoids, anandamide), purine nucleotides and inorganic ions (Ca^{2+} and Mg^{2+}). Thus receptors such as G-protein-coupled receptors (GPCRs) and receptor tyrosine kinases that activate phospholipase C, can modulate TRP channel activity by either hydrolysis of phosphatidylinositol (4,5) bisphosphate (PIP_2), production of diacylglycerol (DAG), or production of inositol (1,4,5) trisphosphate (IP_3), with resultant liberation of Ca^{2+} from intracellular stores [35]. TRP channels act as cellular sensors and are directly activated by physical stimuli such as changes in ambient temperature and mechanical stimuli [36]. Although lacking a conserved series of arginine residues in the S4 domain that form the sensor for transmembrane electrical potential in classical voltage gated ion channels, TRP channels exhibit voltage–dependent current relaxation following depolarization which is modulated by temperature or ligand binding [37].

The TRPC1 channel was the first TRP channel to be identified and cloned [38]. Several TRPC channels have since been identified and these may be divided into three groups on the basis of sequence and functional similarities, TRPC1/4/5, TRPC3/6/7 and TRPC2 [30]. The human TRPC2 gene encodes a non-functional truncated protein [39]. All TRPC channels are highly expressed in human brain with discrete patterns of distribution [40]. The hTRPC1, hTRPC3 and hTRPC5 mRNAs have been found widely expressed at similar levels across most brain regions, with hTRPC5 exhibiting the most CNS-specific expression with ten-fold higher levels in the CNS than in the periphery [40].

The thermo-TRP channels are a subset of TRP channels expressed in primary afferent neurons and cutaneous tissues that respond to distinct thermal thresholds [41]. The thermo-TRP channels include TRPV1–4 channels which are heat activated, and TRPM8 and TRPA1 which are cold activated, the channel phenotype being conferred by the C-terminal domain [42]. The TRPV subfamily may be divided into two groups: TRPV1–4, and TRPV5–6. TRPV1–4 channels are expressed in the nervous

system and share the property of thermosensitivity [43–45], responding to different temperature ranges from moderate to noxious heat. The TRPV1 channel, also known as the capsaicin receptor or vanilloid receptor 1, was first identified in sensory neurons [43,46], but is now known to be widely distributed in both the central and peripheral nervous systems [47–49].

3. Possible links between TRP channels and schizophrenia

Since schizophrenia results from a disorder of the human nervous system, aspects of TRP channel function that might relate to brain development and function are of greatest relevance. Currently there is lack of direct evidence linking TRP channels to schizophrenia. Nevertheless, several aspects of the disorder suggest that TRP channels might play direct or indirect roles in its pathogenesis and symptomatology. In this review possible links between TRP channels and schizophrenia in relation to neurodevelopment, neurochemical mechanisms, in particular dopaminergic and cannabinoid mechanisms, and disorders of thermoregulation and sensation observed in subjects with schizophrenia, are discussed.

3.1. TRPC channels and neurodevelopment

The reduced neuropil found in the cortex in schizophrenia has been attributed to reduced neuronal dendritic arborization. An important recent development of possible relevance to the reduced neuropil found in schizophrenia has been the discovery that TRPC channels play key roles in neurite extension and growth cone guidance [50]. Homomeric TRPC5 channels are rapidly delivered to the plasma membrane following growth factor receptor stimulation [51] and have been shown to control neurite length and growth cone morphology of cultured mouse hippocampal neurons by regulating Ca^{2+} influx [50]. The mechanisms governing the inhibitory role of TRPC5 in neuronal outgrowth have been proposed to involve a protein complex between neuronal calcium sensor-1 (NCS-1) protein and TRPC5 [52]. Ca^{2+} influx through TRPC3 channels has been shown to control selectively growth cone guidance [53].

A diversity of TRPC heteromers has also been found in mammalian brain, with several novel heteromers present in developing brain. Thus it has been proposed that these novel TRPC heteromers might play specific roles in developing brain, particularly as voltage-dependent Ca^{2+} entry channels emerge later than TRPC channels during development [54]. The possibility that formation of particular TRPC heteromers in developing human brain might predispose to schizophrenia is intriguing, and offers a challenge for future investigators.

3.2. TRP channels and synaptic mechanisms

Microarray studies on human postmortem brain have shown a reduction in transcripts encoding proteins involved in the presynaptic release of neurotransmitters in the prefrontal cortex in schizophrenia [55,56]. Furthermore, a study of mRNA from single stellate entorhinal neurons microdissected from post-mortem human brain revealed a reduction in mRNAs encoding synaptic vesicle proteins, synaptophysin and synaptotagmin I and IV, and synaptic plasma membrane proteins, SNAP 23 and SNAP25, whereas an upregulation in mRNA encoding the plasma membrane protein, syntaxin, was found [57].

There is increasing evidence that certain TRP channels play critical roles in fundamental synaptic mechanisms. A critical functional role of agonist-activated TRPC4 channels in the release of GABA from dendrites has been proposed [58]. It has also been demonstrated recently that TRPM7 channels are present in the membrane of cholinergic synaptic vesicles of sympathetic neurons, form molecular complexes with the synaptic vesicle proteins, synapsin I and synaptotagmin I, and directly interact with synaptic vesicular snapin. It was concluded that TRPM7 channel activity is critical for neurotransmitter release in sympathetic neurons [59].

Research on the role of TRP channels in synaptic mechanisms is still at an early stage and it is not possible to predict the role they might play in schizophrenia. Nevertheless, recent discoveries of the critical functional roles played by TRP channels in fundamental mechanisms of neurotransmitter release indicate that investigation of their possible involvement in the pathogenesis of schizophrenia is warranted.

3.3. TRP channels and central dopaminergic mechanisms

Of particular relevance to schizophrenia are observations that TRPV1 channels play a role in dopaminergic mechanisms. Studies in rat and primate brain have shown that TRPV1 channels are widely expressed throughout the neuroaxis, including the cortex, hippocampus, basal ganglia, cerebellum and olfactory bulb as well as in the mesencephalon and hindbrain [47,48]. High expression is found in cell bodies and dendrites of neurons in the hippocampus and cortex, and also on astrocytes and pericytes [60]. However, TRPV1 RNA levels in the CNS are considerably lower than in dorsal root ganglia [61]. Studies on the distribution of TRPV1 in human brain have been more restricted. However, TRPV1 receptors have been found in the third and fifth layers of the human parietal cortex [47].

Until recently, research on TRPV1 channels was predominantly directed at understanding peripheral sensory mechanisms. However, there is growing evidence that TRPV1 channels have functional roles in the CNS. Furthermore, a potential endogenous ligand for the TRPV1 receptor, N-oleoyldopamine, has been found in bovine striatal extracts [62].

In rat brain slices, activation of TRPV1 channels by capsaicin increased the rate of firing of dopamine neurons of the midbrain VTA in a concentration dependent manner. The excitation of dopamine neurons involved a glutamatergic mechanism since it was blocked by superfusion of ionotropic glutamate antagonists [63]. Further, in vivo experiments showed that noxious tail stimulation and microinjection of capsaicin into the VTA transiently increased dopamine release in the nucleus accumbens. Dopamine release by both in vivo tail stimulation and in vitro application of capsaicin were inhibited by the selective TRPV1 receptor antagonist, iodoresiniferatoxin, suggesting a novel role for mesencephalic TRPV1 channels and the dopamine system following noxious stimulation [63].

The finding that many of the dopaminergic cells in the substantia nigra compacta are TRPV1-immunopositive [47,63] suggested that TRPV1 might be involved in the control of movement. In support of this suggestion was the observation that systemic capsaicin suppresses spontaneous locomotion in rats, an effect which was inhibited by the specific TRPV1 antagonist, capsazepine [64]. However, the fact that these drugs were given systemically does not allow firm conclusions to be drawn about the sites of action of capsaicin in this study.

There is less evidence for a role of other TRP channel subfamily members in dopaminergic mechanisms. However, electrophysiological and pharmacological evidence has been obtained implicating TRPC channels in metabotropic glutamate receptor 1 (mGluR1)-mediated excitatory post-synaptic currents (EPSCs) in rat midbrain dopaminergic neurons [65,66].

The results from studies undertaken so far indicate that TRP channels are likely to play an important role in dopaminergic mechanisms in the brain and thus their role in schizophrenia could be of major importance.

3.4. TRP channels and cannabinoid mechanisms

The phylogenetically ancient endocannabinoid system is now emerging as an important regulator of brain development that provides pivotal cues to modulate the fate of neural progenitors [67].

The possible role of cannabis in precipitation of schizophrenia has received considerable attention in recent years. There is increasing acceptance of an association between cannabis use and early onset of the first episode of psychosis in susceptible individuals. The reader is referred to recent reviews [68–73].

Although there is recognition of an association between cannabis use and early onset of psychosis, the mechanisms involved are not clear. Results from recent investigations suggest complex relationships between TRPV1, cannabinoid and dopaminergic mechanisms. Heterodimer formation between CB_1 and D_2 receptors has been identified as a mechanism of cross-talk between these two receptor systems [67]. It is not known whether direct cross-talk occurs between TRPV1 channels and either CB_1 or D_2 receptors, although indirect influences via second messenger signaling systems are highly likely.

The endocannabinoid, anandamide, was initially described as an endogenous agonist for cannabinoid CB_1 receptors, the predominant cannabinoid receptor in the brain [74]. However, anandamide also activates TRPV1 channels at an intracellular site [75] and has been proposed to be an endogenous activator of TRPV1 channels.

Electrophysiological studies have shown that endocannabinoids act as retrograde signaling molecules to modulate glutamate and GABA mediated regulation of the activity in midbrain dopaminergic neurons. Activation of both TRPV1 and CB_1 receptors has been shown to modulate dopamine-mediated locomotion in rats [64]. Interestingly, mice with knockout of the dopamine transporter (DAT), a useful animal model of the hyperdopaminergic state, exhibit hyperactivity and have markedly reduced anandamide levels in the striatum [76]. Administration of indirect endocannabinoids reduced the hyperactivity by action on TRPV1 receptors and not on CB_1 receptors [76].

Immunohistochemical studies have shown a striking similarity between the distribution of TRPV1 and cannabinoid CB_1 receptors in many CNS regions, with coexistence occurring in cell bodies in several regions [77]. TRPV1 and cannabinoid CB_1 receptors coexist in the ventrolateral periaqueductal grey (PAG) neurons of the midbrain, and endocannabinoids may affect descending pain pathways by acting at either CB_1 or TRPV1 receptors [78].

In light of the anatomical and functional overlap between the TRPV1 and cannabinoid receptor systems, it is tempting to suggest, despite the limited evidence available, that TRPV1 channels may be implicated in the actions of cannabinoids in precipitating psychosis, and that ligands for the TRPV1 channels might provide useful new therapeutic strategies.

3.5. TRP channels and thermoregulation

Subjects with schizophrenia commonly show dysregulation of body temperature, with abnormal daily body temperature ranges and an impaired ability to compensate for heat stress, possibly involving both central and peripheral mechanisms [79–82]. Although studies in subjects with schizophrenia are often confounded by neuroleptic drug treatment, disorder of thermoregulation has been confirmed in drug-free subjects [80].

The importance of the preoptic area of the anterior hypothalamus in thermoregulation has been recognized for many years. Dopamine agonists induce hypothermia in humans and animals and midbrain dopaminergic mechanisms have been shown to play an important role in thermoregulation [83]. Moreover, a complex central regulatory thermostat mechanism, involving serotoninergic and dopaminergic mechanisms, has been described [82]. Evidence for a role of both dopamine D_1 and D_2 receptors in the anteroventral preoptic area has been obtained in rats, dopamine D_2 receptors being mainly involved in the maintenance of body temperature in euthermia [84].

Injection of capsaicin into the preoptic area also causes hypothermia in vivo, and capsaicin desensitization induces impaired ability to thermoregulate against heat [85]. Whilst the mechanisms are not clear they are likely to be complex involving both central and peripheral mechanisms. Studies using whole cell patch-clamp recordings from neurons in the medial preoptic nucleus have shown that capsaicin enhanced the frequency of spontaneous glutamatergic excitatory postsynaptic currents and also of GABAergic inhibitory postsynaptic currents [86]. Injection of capsaicin into the anterior hypothalamus of knockout mice lacking the TRPV1 channel did not produce a change in body temperature providing evidence that capsaicin induces its central effects on thermoregulation via action on TRPV1 channels [87].

Other TRPV channels are also likely to play a role in thermoregulation. Temperature sensitive TRPV3 and TRPV4 channels are expressed in dopaminergic neurons of the substantia nigra pars compacta [88]. Indeed, the neuroprotective effect of hypo-

thermia has been attributed partly to the closing of TRPV3 and/or TRPV4 channels [89].

The similarity between the thermoregulatory deficit in animals following capsaicin desensitization and that observed in schizophrenia is noteworthy. However, the possible interrelationships between TRPV channels, dopamine, thermoregulation and schizophrenia remain to be explored.

3.6. TRP channels and sensory processes

Much research on TRP channels is currently focused on their involvement in sensory processes, particularly in relation to primary afferent neuron function and nociception. Members of the TRPM, TRPA and TRPV channel subfamilies activate sensory mechanisms. Nevertheless, it should be noted that understanding of the physiological and pathophysiological role of even the most widely researched TRP, TRPV1, is limited.

3.6.1. TRPM8 and TRPA1 channels

The TRPM8 channel of the TRPM subfamily (melastatin) is expressed in sensory neurons and is activated by cold, menthol and icilin and has been proposed to function as a cold thermosensor [90–93]. The TRPA1 channel, distinguished by the presence of multiple ankyrin repeats in its N terminus, is also expressed by sensory neurons. Although first described as a cold-sensitive, nonselective cation channel [94], studies in knockout mice have not supported an essential role for TRPA1 in the detection of noxious cold [95]. TRPA1 is now considered to function as a ligand-gated channel in sensory neurons, that is activated by pungent natural compounds including mustard oil, garlic and cannabinoids, and by endogenous inflammatory mediators and environmental irritants [95], and inhibited by menthol [96]. TRPA1 is also regulated by PLC-coupled receptors, and is possibly the molecular mechanism for the paradoxical perception of noxious cold as burning pain [97–99].

3.6.2. TRPV channels

Investigation in the field of TRP channels and sensory mechanisms has been dominated by studies on the role of the TRPV subfamily in sensory processes.

In the peripheral nervous system TRPV1 channels are expressed by a class of neuropeptide-containing, unmyelinated primary afferent neuron involved in nociception, axon reflex flare and neurogenic inflammation [100,101]. These neurons are glutamatergic and contact spinal neurons that co-express tachykinin NK_1 receptors and ionotropic (NMDA or AMPA) glutamate receptors [102]. The TRPV1 channel is considered to play a key role in nociception and thus research has been driven by the prospect of development of novel anti-nociceptive or anti-inflammatory agents [103]. Since its cloning in 1997 [43], considerable understanding of the amino acids of the TRPV1 protein involved in specific functions such as capsaicin action, heat activation, proton action, desensitization and modulation by lipids, has been gained.

TRPV1 channels are activated polymodally by chemicals including capsaicin and resiniferatoxin, the endocannabinoid, anandamide [104], eicosanoids, 2-aminoethoxydiphenyl borate (2-APB) and camphor, as well as by heat, H^+ [43,46,105] and polyamines [106]. Activation results in weakly Ca^{2+}-selective, outwardly rectifying, cation currents [43]. TRPV1 channels are sensitized by PKA, PKC, receptor-activated PLC, extracellular cations and polyamines [106–111]. A novel human TRPV1 RNA splice variant, TRPV1b, which forms functional ion channels that are activated by noxious temperature but not by capsaicin or protons, has been reported, and may contribute to thermal nociception [112].

Genetic influences on variability of human acute experimental pain sensitivity are increasingly being recognized, and some reports indicate that genetic differences in TRPV1 channel structure or level of expression might be important. Kim et al. [113] reported that female European Americans with the TRPV1 Val (585) Val allele showed longer cold withdrawal times. A human case of decreased expression of TRPV1 resulting in total loss of sensitivity to capsaicin has been reported [114]. TRPV1 channels have been shown to play an important role in pain mediated by central sensitization, thus indicating that the role of TRPV1 channels in pain mechanisms may involve both peripheral and central components [115].

Recently a regulatory protein, Fas-associated factor 1 (FAF1), that is coexpressed with, and forms an integral component of, the TRPV1 channel complex, has been found [116]. Silencing FAF1 by RNA interference augments capsaicin-sensitive current in native sensory neurons and it has been proposed that FAF1 modulates the sensitivity of TRPV1 channels to noxious stimuli [116]. This finding might explain some of the differences that have been found between TRPV1 channels and native capsaicin receptors. Growth factors also play a role in the regulation of TRPV1 channel function. Neuropeptide release in trigeminal ganglion neurons in vitro by capsaicin-induced activation of TRPV1 channels has been shown to be significantly increased by chronic treatment with nerve growth factor (NGF) and to a lesser extent by glial cell line-derived neurotrophic factor (GDNF) [117]. Although the pathophysiological significance of these modulatory mechanisms has not yet been explored, their discovery points to a major field of future research.

Activation of TRPV1 channels by vanilloid agonists results in nociception and neurogenic inflammation mediated primarily by the neuropeptides, substance P and calcitonin gene related peptide (CGRP), released from the peripheral terminals of the activated primary afferent neurons [100,101]. Mice with TRPV1 gene disruption exhibit loss of responsiveness to capsaicin, protons, and PKC activation, and deficit in neuropeptide release, but little change in nocifensive behaviour induced by heat, inflammatory or neuropathic mechanical hyperalgesia [118,119]. Thus, although TRPV1 channels are not responsible for normal nociceptive heat responses, they play an essential role in thermal hyperalgesia and neuropeptide release, and thus in neurogenic inflammation.

Desensitization of TRPV1 channels by capsaicin has been widely exploited in pharmacological investigations into sensory mechanisms. If given to neonatal rats, capsaicin produces lifelong loss of a high proportion of capsaicin-sensitive primary afferent neurons [120], the majority of which are unmyelinated [121]. Desensitization is the major mechanism by which cap-

saicin produces its paradoxical analgesic action. Capsaicin-induced desensitization of TRPV1 channels is dependent on extracellular Ca^{2+}, and disruption of binding of the Ca^{2+}-binding protein, calmodulin, to the C-terminus of the TRPV1 channel prevents desensitization [122]. PKA reduces TRPV1 desensitization by phosphorylation of Ser 116 [123], whereas phosphorylation of TRPV1 at S800 by PKCepsilon increases the sensitivity of desensitized TRPV1 [124].

3.7. Effect of neonatal capsaicin treatment on rat brain development

The possibility that the somatosensory system might be involved in the pathogenesis of schizophrenia was suggested by two observations, firstly, that deficits in pain sensation are present in subjects with schizophrenia [125,126] and their relatives [127], and secondly, that vascular responsiveness is altered as shown by reduced flare responses to niacin (nicotinic acid) and methylnicotinate in many subjects with the disorder and their relatives [128,129]. The subset of primary afferent neurons involved in both pain and flare responses are the small diameter primary afferent fibres that are sensitive to the neurotoxic action of capsaicin. These observations suggested that capsaicin-sensitive primary afferent neurons might be abnormal in schizophrenia.

If a population of primary afferent neurons were abnormal in schizophrenia, the question arises as to how such an abnormality could give rise to schizophrenia. Studies in developmental neurobiology have shown that neonatal somatosensory deprivation such as that induced by whisker trimming in the mouse whisker barrel model, results in reduced synaptic density in the barrel cortex [130]. The capsaicin-sensitive primary afferent neurons are widely distributed throughout the body and it might be expected that even a small deficit in input via these neurons throughout development could result in reduced synaptic density in several cortical areas and 'reduced neuropil' such as that seen in the brains of subjects with schizophrenia [15,16].

The possibility that intrinsic somatosensory deprivation affects brain development was recently tested in rats treated as neonates with capsaicin to destroy a population of TRPV1-expressing primary afferent neurons, on the assumption that this would give rise to an intrinsic somatosensory deprivation [131]. At 5–7 weeks the rats treated as neonates with capsaicin had increased locomotor activity in a novel environment. Although they had normal body weight, the male rats had reduced brain weight. The capsaicin-treated rats also had reduced hippocampal and coronal cross-sectional area, reduced cortical thickness and increased neuronal density in several cortical areas [131]. These changes are similar to those found in schizophrenia. The brain changes were maintained into adulthood (11–12 weeks), indicating that neonatal capsaicin treatment produced long-lasting changes in the rat brain (Newson et al. unpublished). Furthermore, cutaneous inflammatory responses to methylnicotinate were reduced in capsaicin-treated rats, showing that the response to methylnicotinate had a neurogenic component (Newson et al. unpublished).

The findings of Newson et al. [131] suggest that the neonatal capsaicin-treated rat might be a useful animal model of schizophrenia. However, the study was based on the assumption that the principle site of action of capsaicin was the TRPV1 channel on the primary afferent neuron. Although the primary afferent neuron would undoubtedly have been a major target of neonatal capsaicin treatment in this study, the possibility that capsaicin produced the observed brain changes by actions in the CNS must be considered. A neurotoxic action of capsaicin on central TRPV1 channels, similar to that observed in the peripheral sensory system, was considered unlikely as neonatal capsaicin treatment has been shown not to affect TRPV1 receptor mRNA expression in rat brain [47]. However, action on target molecules other than TRPV1 channels might have occurred. A difficulty with the use of capsaicin as a tool, is its widespread action on membrane proteins other than TRPV1 channels such as voltage-dependent sodium channels. Capsaicin and the capsaicin antagonist, capsazepine have been shown to regulate these proteins by altering lipid bilayer elasticity [132].

Older studies had shown that the neurotoxic effect of capsaicin is not limited to somatosensory neurons. Although other neurons in the periphery, such as lower motor neurons, were not affected, Perez et al. [133] showed that olfactory afferents were sensitive to the neurotoxic effects of neonatal capsaicin treatment, and that body, brain and olfactory bulb weights were reduced in capsaicin-treated rats. Furthermore, a study of the effects of systemic capsaicin on the CNS of 10-day-old and adult rats showed that many areas not previously known to receive primary afferent input, including the interpeduncular nucleus, raphe nuclei, hypothalamic and septal nuclei, accumbens shell and olfactory bulb, showed evidence of degenerating terminals [134,135]. The long-term functional significance of this effect is unknown as several of these CNS areas are not responsive to capsaicin in the adult rat [135]. Indeed, some of these degenerative effects might have resulted directly or indirectly from degeneration of vagal sensory neurons [134].

Studies on the effects of capsaicin in adult rats have shown that capsaicin does not affect the permeability of the blood–brain barrier [136], and that capsaicin causes degeneration of central terminals of primary afferent neurons in the adult CNS only when applied centrally [137]. However, in neonatal rats the blood–brain barrier is more permeable and it is likely that capsaicin would enter the brain and have CNS actions. Whether these actions have long-term consequences for brain development and function remains to be determined.

Despite the limitations of the study by Newson et al. [131], the simplest explanation for the findings is that neonatal capsaicin treatment resulted in somatosensory deprivation which affected brain development. Further studies are required to determine whether the changes produced in rat brain by neonatal capsaicin treatment result from somatosensory deprivation or direct actions of capsaicin within the brain. Such information will be required before the neonatal capsaicin-treated rat is accepted as a useful animal model of schizophrenia.

4. Conclusion

Schizophrenia remains a major challenge to neuroscience and to pharmacotherapeutics. The affliction of the unique human

higher nervous system has resulted in lack of validated animal models [138] and has hindered rational drug development. Recognition of the probable polygenic nature of schizophrenia and the role of environmental factors has not yet led to greater understanding of the fundamental pathophysiology of schizophrenia. The discovery of neuropathological changes in many brain regions and of changes in several neurotransmitter systems has also not clarified the aetiology of the disorder. The number of brain changes that have been described makes it tempting to speculate that the cause of schizophrenia is a subtle abnormality in a fundamental cellular process, such as TRP channel signaling, that results in many consequent neurochemical and epigenetic changes. On current evidence it seems unlikely that a single gene disruption in a TRP channel would be directly responsible. Nevertheless, the possibility remains that an environmental factor might precipitate disruption or silencing of a single gene such as a TRP channel gene, hitherto unsuspected of involvement in schizophrenia, with downstream neurodevelopmental and neurochemical consequences resulting in the disorder. Studies on mice deficient in likely TRP channel candidates such as TRPV1 channels, have so far concentrated on the peripheral sensory deficits [139]. Further exploration of the effects of TRP channel deficiencies on the brain and behaviour are warranted.

Study of the role of TRP channels is still at an early stage and few firm conclusions can be reached about their possible role in a disorder as complex and poorly understood as schizophrenia. Nevertheless, the possible links between TRP channels, neurodevelopment and the neurochemical and pathophysiological mechanisms involved in schizophrenia, are tantalizing, and give rise to the prospect that investigation of these links might yield a new understanding of schizophrenia and brain mechanisms in general with resultant therapeutic advances.

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